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NEWS 6	JAN 13	New IPC 8 SEARCH, DISPLAY, and SELECT enhancements added to INPADOC
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NEWS 22	MAR 22	EMBASE is now updated on a daily basis
NEWS 23	APR 03	New IPC 8 fields and IPC thesaurus added to PATDPAFULL
NEWS 24	APR 03	Bibliographic data updates resume; new IPC 8 fields and IPC thesaurus added in PCTFULL
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=> s HA-1 peptide
L1 47 HA-1 PEPTIDE

=> s l1 and VLHDDLLEA
L2 8 L1 AND VLHDDLLEA

=> dup remove l2
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L3 2 DUP REMOVE L2 (6 DUPLICATES REMOVED)

=> d l3 1-2 cbib abs

L3 ANSWER 1 OF 2 MEDLINE on STN DUPLICATE 1
2000166344. PubMed ID: 10703604. Molecular modeling of the minor histocompatibility antigen **HA-1 peptides** binding to HLA-A alleles. Ren E C; Kangueane P; Kolatkar P; Lin M T; Tseng L H; Hansen J A. (Department of Microbiology, WHO Collaborating Center for Immunology, National University of Singapore, Singapore.. micrenec@nus.edu.sg) . Tissue antigens, (2000 Jan) Vol. 55, No. 1, pp. 24-30. Journal code: 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.

AB Mismatch of the minor histocompatibility antigen HA-1 has been shown to correlate with graft-versus-host disease in HLA-matched sibling marrow transplants. The HA-1H peptide (**VLHDDLLEA**) that generates this response is known to be presented by HLA-A*0201. In order to understand the interaction of **HA-1 peptides** with other HLA-A alleles, we have used the LOOK interface to construct molecular models of both HA-1H peptide (**VLHDDLLEA**) and HA-1R peptide (VLRDDLLEA) binding with 103 HLA-A alleles. The results show that in addition to A*0201, 21/103 other HLA-A alleles should be able to bind HA-1H peptide but not HA-1R peptide. Based on the modeled predictions, HLA alleles can be categorised into 4 groups with respect to their interaction with **HA-1 peptides**: Group 1 - bind HA-1H peptide but not HA-1R peptide; Group 2 - bind HA-1R peptide but not HA-1H peptide; Group 3 - bind both HA-1H and HA-1R peptides; Group 4 - bind neither peptide. These predicted binding patterns of **HA-1 peptides** will be useful as an aid for defining a wider pool of HLA-A alleles in which HA-1 disparities among donor-recipient

pairs can be investigated.

L3 ANSWER 2 OF 2 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN DUPLICATE 2
1999342032 EMBASE Clinical potential of the **HA-1** **peptide**, a minor histocompatibility antigen. Expert Opinion on Therapeutic Patents Vol. 9, No. 10, pp. 1437-1441 1999.
Refs: 25.
ISSN: 1354-3776. CODEN: EOTPEG
Pub. Country: United Kingdom. Language: English. Summary Language: English.
Entered STN: 19991021. Last Updated on STN: 19991021
AB Minor histocompatibility (H) antigens are the targets of host versus graft (HVG), graft versus host (GVH) and graft versus leukaemia (GVL) immune responses following transplantation of organs or tissues between donor/recipient pairs matched for transplantation antigens encoded by the major histocompatibility complex (MHC: HLA in humans). There is a particular clinical problem in predicting and treating GVH disease, which occurs in a significant proportion of bone marrow transplant (BMT) patients, even those with HLA-identical sibling donors. However, many of these recipients receive BMT as part of the treatment for leukaemia and there is a correlation in them between harmful GVH and potentially therapeutic GVL, implying the same target antigens. The molecular identity of minor H antigens is therefore a key issue. This patent describes the recent identification of one of the human minor H antigen (HA-1) and proposes methods for using the nonameric peptide identified, **VLHDDLLEA**, or analogues of it, to modulate HVG and GVH responses, to promote GVL and, with knowledge of the polymorphism of the encoding gene, to type BMT recipients and their potential donors for presence of the antigen.

=> s l1 and VLRDDLLEA
L4 5 L1 AND VLRDDLLEA

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L5 1 DUP REMOVE L4 (4 DUPLICATES REMOVED)

=> d l5 cbib abs

L5 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2000166344. PubMed ID: 10703604. Molecular modeling of the minor histocompatibility antigen **HA-1 peptides** binding to HLA-A alleles. Ren E C; Kangueane P; Kolatkar P; Lin M T; Tseng L H; Hansen J A. (Department of Microbiology, WHO Collaborating Center for Immunology, National University of Singapore, Singapore.. micrenec@nus.edu.sg) . Tissue antigens, (2000 Jan) Vol. 55, No. 1, pp. 24-30. Journal code: 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.
AB Mismatch of the minor histocompatibility antigen HA-1 has been shown to correlate with graft-versus-host disease in HLA-matched sibling marrow transplants. The HA-1H peptide (VLHDDLLEA) that generates this response is known to be presented by HLA-A*0201. In order to understand the interaction of **HA-1 peptides** with other HLA-A alleles, we have used the LOOK interface to construct molecular models of both HA-1H peptide (VLHDDLLEA) and HA-1R peptide (**VLRDDLLEA**) binding with 103 HLA-A alleles. The results show that in addition to A*0201, 21/103 other HLA-A alleles should be able to bind HA-1H peptide but not HA-1R peptide. Based on the modeled predictions, HLA alleles can be categorised into 4 groups with respect to their interaction with **HA-1 peptides**: Group 1 - bind HA-1H peptide but not HA-1R peptide; Group 2 - bind HA-1R peptide but not HA-1H peptide; Group 3 - bind both HA-1H and HA-1R peptides; Group 4 - bind neither peptide. These predicted binding patterns of **HA-**

1 peptides will be useful as an aid for defining a wider pool of HLA-A alleles in which HA-1 disparities among donor-recipient pairs can be investigated.

=> s l1 and cytotoxic T cell
L6 28 L1 AND CYTOTOXIC T CELL

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L7 9 DUP REMOVE L6 (19 DUPLICATES REMOVED)

=> d l7 1-9 cbib abs

L7 ANSWER 1 OF 9 CAPLUS COPYRIGHT 2006 ACS on STN
2004:571330 Document No. 141:258993 Artificial antigen-presenting constructs efficiently stimulate minor histocompatibility antigen-specific cytotoxic T lymphocytes. Oosten, Liesbeth E. M.; Blokland, Els; Van Halteren, Astrid G. S.; Curtsinger, Julie; Mescher, Matthew F.; Falkenburg, J. H. Frederik; Mutis, Tuna; Goulmy, Els (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Neth.). Blood, 104(1), 224-226 (English) 2004. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.
AB Cytotoxic T lymphocytes (CTLs) specific for hematopoietic-restricted minor histocompatibility antigens (mHags) are important reagents for adoptive immunotherapy of relapsed leukemia after allogeneic stem cell transplantation. However, expansion of these CTLs to therapeutic nos. is often hampered by the limited supply of antigen-presenting cells (APCs). Therefore, the authors evaluated whether cell-sized latex beads coated with HLA/mHag complexes HLA-A2/HA-1 or HLA-A2/HA-2 and recombinant CD80 and CD54 mols. can replace professional APCs. The artificial antigen-presenting constructs (aAPCs) effectively stimulated HA-1-and HA-2-specific CTL clones as shown by ligand-specific expansion, cytokine production, and maintenance of cytotoxic activity, without alteration of CTL phenotype. Furthermore, HA-1-specific polyclonal CTL lines were enriched as efficiently by aAPCs as by autologous **HA-1 peptide**-pulsed dendritic cells. Thus, aAPCs coated with HLA/mHag complexes, CD80, and CD54 may serve as tools for in vitro enrichment of immunotherapeutic mHag-specific CTL lines.

L7 ANSWER 2 OF 9 MEDLINE on STN DUPLICATE 1
2002459659. PubMed ID: 12218130. Identification of a novel HLA-B60-restricted T cell epitope of the minor histocompatibility antigen HA-1 locus. Mommaas Bregje; Kamp Janine; Drijfhout Jan-Wouter; Beekman Nico; Ossendorp Ferry; Van Veelen Peter; Den Haan Joke; Goulmy Els; Mutis Tuna. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.) Journal of immunology (Baltimore, Md. : 1950), (2002 Sep 15) Vol. 169, No. 6, pp. 3131-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB The polymorphic minor histocompatibility Ag HA-1 locus encodes two peptides, HA-1(H) and HA-1(R), with a single amino acid difference. Whereas the immunogenicity of the HA-1(R) allele has not yet been shown, the nonameric HA-1(H) peptide induces HLA-A2-restricted **cytotoxic T cells** in vivo and in vitro. It is not known whether the mHag HA-1(H) or HA-1(R) associates with other HLA class I molecules. Therefore, the polymorphic regions of both HA-1 alleles were analyzed to identify HLA class I binding peptides that are properly processed by proteasomal degradation. Peptide binding analyses were performed for all nonameric HA-1(H/R) peptides for binding to nine HLA class I molecules with >10% prevalence in the Caucasian population and for seven nonameric/decameric HA-1(H/R) peptides predicted to bind to HLA-A3, -B14, and -B60. Only the nonameric KECVL(H)/(R)DDL and decameric KECVL(H)/(R)DDLL peptides showed strong and stable binding to HLA-B60. In vitro digestion of 29-aa-long **HA-1 peptides**

by purified 20S proteasomes revealed proper cleavage at the COOH termini of both HLA-B60 binding HA-1(H) and HA-1(R) peptides. In subsequent analyses, dendritic cells pulsed with the nonameric HA-1(R) peptide did not induce CTLs that recognize the natural HLA-B60/HA-1(R) ligand. In contrast, dendritic cells pulsed with the nonameric HA-1(H) peptide induced IFN-gamma-secreting T cells specific for the natural HLA-B60/HA-1(H) ligand in three HLA-B60(+) HA-1(RR) individuals, demonstrating the immunogenicity of the HLA-B60/HA-1(H) ligand. In conclusion, this study shows a novel HLA-B60-restricted T cell epitope of the minor histocompatibility Ag HA-1 locus.

L7 ANSWER 3 OF 9 MEDLINE on STN DUPLICATE 2

2002348185. PubMed ID: 12091347. Generation of minor histocompatibility antigen HA-1-specific **cytotoxic T cells** restricted by nonself HLA molecules: a potential strategy to treat relapsed leukemia after HLA-mismatched stem cell transplantation. Mutis Tuna; Blokland Els; Kester Michel; Schrama Ellen; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Blood, (2002 Jul 15) Vol. 100, No. 2, pp. 547-52. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Successful stem cell transplantation (SCT) across HLA barriers can be performed with cord blood, megadoses of stem cells, or with nonmyeloablative conditioning strategies. Because the HLA-mismatched transplants are often T-cell depleted, leukemia relapse rates are high. Treatment of relapsed leukemia after HLA-mismatched SCT is difficult. A novel potential strategy to treat relapsed leukemia after HLA-mismatched SCT is the use of patients' mismatched HLA molecules as antigen-presenting molecules to generate hematopoietic system-specific **cytotoxic T cells** (CTLs) from the stem cell donor. Adoptive transfer of these hematopoietic system-specific CTLs that are restricted by nonself HLA molecules may eliminate leukemia without affecting the patient's nonhematopoietic cells or donor hematopoietic cells. We investigated the feasibility of this strategy using the hematopoietic system-specific minor histocompatibility antigen HA-1, which is known to induce HLA-A2-restricted CTLs. HLA-A2(-) peripheral blood mononuclear cells were stimulated with HLA-A2(+) T2 cells pulsed with synthetic **HA-1 peptide** or with dendritic cells transduced with the HA-1 cDNA. Tetrameric HLA-A2/**HA-1 peptide** complexes were used to monitor and enrich HA-1-specific CTLs. In the alloreactive cultures, HA-1-specific CTLs were enriched up to 7% by 3 rounds of antigen-specific stimulations and up to 87% by fluorescence-activated cell sorting of tetramer-positive T cells. The HA-1-specific CTLs showed specific lysis of the relevant target cells, including leukemic cells. Because the polyclonal CTL cultures also contained natural killer cells and allo-HLA-A2-specific CTLs, CTL clones were generated that showed the expected HA-1 specificity only. Thus, HA-1-specific CTLs restricted by nonself HLA-A2 molecules can be generated in an HLA-A2-mismatched setting.

L7 ANSWER 4 OF 9 MEDLINE on STN DUPLICATE 3

2002472540. PubMed ID: 12234166. Efficient induction of minor histocompatibility antigen HA-1-specific **cytotoxic T-cells** using dendritic cells retrovirally transduced with HA-1-coding cDNA. Mutis Tuna; Ghoreschi Kamran; Schrama Ellen; Kamp Janine; Heemskerk Mirjam; Falkenburg J H Frederik; Wilke Martina; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, (2002) Vol. 8, No. 8, pp. 412-9. Journal code: 9600628. ISSN: 1083-8791. Pub. country: United States. Language: English.

AB **Cytotoxic T-cells** (CTLs) specific for the hematopoietic system-restricted minor histocompatibility antigen (mHag) HA-1 efficiently lyse HA-1-positive leukemic cells without affecting

nonhematopoietic cells. HA-1-specific CTLs are thus potential tools for adoptive immunotherapy of relapsed leukemia after HLA-matched-HA-1-mismatched stem cell transplantation (SCT). In vitro generation of HA-1-specific CTLs from SC donors is possible using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide** as stimulator cells. However, this approach requires at least 6 weeks of in vitro culturing under GMP (good manufacturing practice) conditions. Our data show that in vitro induction of HA-1-specific CTLs is more rapid with the use of DCs that are retrovirally transduced with the HA-1 complementary DNA. Retrovirally transduced DCs showed functional and long-term stable expression of the HA-1 CTL epitope in primary CTL cultures. In 4 SC donors, HA-1-transduced DCs induced HA-1-specific CTLs in 14 to 21 days. The in vitro-generated CTL lines contained 6% to 9% T-cells that stained brightly with tetrameric HLA-A2/**HA-1 peptide** complexes (HA-1(A2) tetramer) and showed significant lysis of HA-1+ leukemic cells. The CTL induction procedure using peptide-pulsed DCs was less effective and required 28 to 35 days of T-cell culture. Thus, sustained presentation of mHag HA-1 by retrovirally transduced DCs facilitates the in vitro induction of HA-1-specific CTLs.

L7 ANSWER 5 OF 9 MEDLINE on STN DUPLICATE 4

2002425399. PubMed ID: 12163564. The hematopoietic system-specific minor histocompatibility antigen HA-1 shows aberrant expression in epithelial cancer cells. Klein Christoph A; Wilke Martina; Pool Jos; Vermeulen Corine; Blokland Els; Burghart Elke; Krostina Sabine; Wendler Nicole; Passlick Bernward; Riethmueller Gert; Goulmy Els. (Department of Immunology, Klinikum Innenstadt, Ludwig-Maximilians University, 80336 Munich, Germany.. E.A.J.M.Goulmy@lumc.nl) . The Journal of experimental medicine, (2002 Aug 5) Vol. 196, No. 3, pp. 359-68. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Allogeneic stem cell transplantation (SCT) can induce curative graft-versus-tumor reactions in patients with hematological malignancies and solid tumors. The graft-versus-tumor reaction after human histocompatibility leukocyte antigen (HLA)-identical SCT is mediated by alloimmune donor T cells specific for polymorphic minor histocompatibility antigens (mHags). Among these, the mHag HA-1 was found to be restricted to the hematopoietic system. Here, we report on the HA-1 ribonucleic acid expression by microdissected carcinoma tissues and by single disseminated tumor cells isolated from patients with various epithelial tumors. The **HA-1 peptide** is molecularly defined, as it forms an immunogenic peptide ligand with HLA-A2 on the cell membrane of carcinoma cell lines. HA-1-specific **cytotoxic T cells** lyse epithelial tumor cell lines in vitro, whereas normal epithelial cells are not recognized. Thus, HA-1-specific immunotherapy combined with HLA-identical allogeneic SCT may now be feasible for patients with HA-1(+) carcinomas.

L7 ANSWER 6 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2003:357430 Document No.: PREV200300357430. Non-Availability of Clinical Grade Reagents Prohibits the Clinical Application of In Vitro Cultured Peptide-Specific Cytotoxic T Lymphocytes(CTL). Marijt, W. A. F. [Reprint Author]; Bergen, C. A. M. van [Reprint Author]; Hoorn, M. A. W. G. van [Reprint Author]; Muijsenberg, J. W. van den [Reprint Author]; Willemze, R. [Reprint Author]; Falkenburg, J. H. F. [Reprint Author]. Hematology, Leiden University Medical Center, Leiden, Netherlands. Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 3295. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB CTL with specificity for the hematopoiesis-associated mHag HA-1 and/or HA-2 can be generated from healthy stem cell donors using mature dendritic cells (DC) loaded with HA-1 or -2 peptide as stimulator cells. Administration of such CTL instead of unmanipulated DLI to patients with relapsed leukemia after alloSCT may induce a GVL effect with little or no

GVHD. Clinical grade DC can be generated from CD14+ or CD34+ cells cultured in the presence of GM-CSF, SCF, IL-4 and/or TNF. However, maturation of CD14 or CD34 derived DC is essential for efficient induction of mHag specific CTL from unprimed individuals. By addition of various maturation factors such as alpha-IFN, TNF, polyI:C, or CPG to DC during the last 2 days of culture, partial maturation can be obtained as shown by upregulation of CD40, and CD86, but often only modest or no upregulation of CD80 and CD83 is found. Unfortunately, we were not able to frequently induce a primary response and generate sufficient numbers of mHag specific CTL using partially maturated peptide loaded DC as stimulator cells. In contrast, when naive T cells were stimulated with HA-1 loaded DC that were fully maturated by addition of CD40-L transfected mouse fibroblasts (CD40-L cells) resulting in high expression of CD80 and CD83 molecules on a higher number of DC (mean fluorescence intensity 871+-461 and 229+-35 in the presence of CD40-L cells, versus 162+-39 and 47+-20, respectively, without CD40-L cells) large numbers of highly **cytotoxic T cells** could be generated consisting of up to 45% HA-1 specific T cells as demonstrated by staining with HLA-A2/HA-1 tetramers. Cytotoxicity assays showed 55% lysis of PHA blasts loaded with **HA -1 peptide**, 30% lysis of PHA blasts expressing endogenous **HA-1 peptide** and no lysis of HA-1 negative PHA blasts (E:T ratio of 1:1). Production of IL-12 by these mature DC was high (1988+-883 pg/mL) emphasizing their capacity to induce a primary immune response. However, CD40-L cells are not approved for clinical use. Therefore, we attempted to use alternative maturation stimuli that are approved for clinical use such as DKTP (diphtheria, whooping cough, tetanus toxoid, and polio) vaccine, or tetanus toxoid (TT) vaccine. Addition of DKTP or TT to DC cultures induced 30-40% less upregulation of CD80- and CD83 molecules compared to maturation with CD40-L cells. Furthermore, production of IL-12 was much lower (6+-10 pg/mL) and IL-10 production was relatively high. Using DKTP maturated, HA-1 loaded DC only limited numbers of specific CTL could be induced. An alternative to the use of CD40-L cells might be the addition of effective amounts clinical grade IL-12 to the CTL cultures to bypass the lack of fully matured DC. However, clinical grade IL-12 has not been made available. In conclusion, we show that it is feasible to fully maturate CD14 and CD34 derived DC with CD40-L cells as measured by the high upregulation of CD80 and CD83 expression and substantial production of IL-12 resulting in the generation of HA-1 tetramer+ CTL and lysis of HA-1+ target cells. Alternative maturational stimuli, such as DKTP or TT, which are approved for clinical use could not replace CD40-L cells. Currently, one of the major obstacles for efficient clinical application of antigen specific cellular immunotherapy to treat patients with relapsed leukemia after alloSCT is the unavailability of clinical grade reagents.

L7 ANSWER 7 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:312013 Document No.: PREV200100312013. Efficient in vitro induction of minor histocompatibility antigen HA-1 specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with HA-1 coding gene segment. Mutis, Tuna [Reprint author]; Wilke, Martina [Reprint author]; Ghoreschi, Kamran; Schrama, Ellen [Reprint author]; Kamp, Janine [Reprint author]; Heemskerk, Mirjam; Falkenburg, J. H. Frederik; Goulmy, Els [Reprint author]. Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 582a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The minor histocompatibility antigen (mHag) HA-1 is a hematopoietic system specific polymorphic antigen that can be recognized by **cytotoxic T cells** (CTLs) in the context of HLA-A2. HA-1 specific CTLs exhibit strong anti-leukemia reactivity by lysing HA-1 positive leukemic cells and their clonogenic precursors without affecting non-hematopoietic cells. Adoptive transfer of in vitro generated HA-1

specific CTLs into HA-1 positive patients with relapsed leukemia may therefore be curative with a low risk of graft versus host disease (GvHD). We have recently shown the feasibility of in vitro generation of HA-1 specific CTLs from HA-1 negative individuals using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide.**
However, under GMP conditions, HA-1 CTLs can not be generated from some donors using peptide pulsed DCs. We therefore investigated whether generation of HA-1 specific CTLs is more effective using DCs that are retrovirally transduced to express the HA-1 antigen. The 312 base pair gene segment coding for the HA-1 CTL epitope was cloned into the retroviral vector LZRS. This vector was transduced into several cell lines including CD34+ DC progenitors with 10-40% efficiency. All retrovirally transduced cells showed stable and functional expression of the HA-1 CTL epitope. CD34+ DC progenitors differentiated normally into immature DCs within 10-12 days and induced strong in vitro HA-1 specific CTL responses in four out of six HA-1 negative healthy unprimed individuals. The CTL lines contained 6-10% HA-1 specific CTLs as determined by HLA-A2/**HA-1 peptide** tetramers.
The induction of HA-1 specific CTLs by retrovirally transduced DCs required only one or two rounds of restimulation whereas CTL induction by peptide pulsed DCs required three to five rounds of restimulations. During the CTL induction, the retrovirally transduced DCs were detected at least seven days in the cultures and retained their immature phenotype. Our results demonstrate that retrovirally transduced immature DCs effectively induce HA-1 specific CTL responses through their continuous presentation of the HA-1 T cell epitope to unprimed T cell precursors.

L7 ANSWER 8 OF 9 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
1998:511549 Document No.: PREV199800511549. HA-1 and the SMCY-derived peptide FIDSYICQV (H-Y) are immunodominant minor histocompatibility antigens after bone marrow transplantation. Rufer, Nathalie; Wolpert, Elisabeth; Helg, Claudine; Tiercy, Jean-Marie; Gratwohl, Alois; Chapuis, Bernard; Jeannet, Michel; Goulmy, Els; Roosnek, Eddy [Reprint author]. Unite d'Immunol. Transplantation, Hopital Cantonal Univ. Geneve, 24 rue Micheli-du-Crest, CH-1211 Geneve 14, Switzerland. Transplantation (Baltimore), (Oct. 15, 1998) Vol. 66, No. 7, pp. 910-916. print.
CODEN: TRPLAU. ISSN: 0041-1337. Language: English.
AB Background. Allogeneic bone marrow donors can be incompatible at different levels. Even HLA-identical pairs will be still incompatible for numerous minor histocompatibility antigens (mHag). Nevertheless, some incompatibilities are found to be associated with an increased risk of graft-versus-host disease (GVHD), which could be related to the way the immune system recognizes these antigens. Methods. We determined the specificity of **cytotoxic T-cell** clones
isolated during acute GVHD or during bone marrow graft rejection in patients (n=14) transplanted with marrow from donors who were histoincompatible for different minor and/or major histocompatibility antigens. Results. We found a clear hierarchy among the different types of histoincompatibilities. In three combinations mismatched for a class I allele, all 27 clones isolated during GVHD were specific for the incompatible HIA molecule. In the 11 class I-identical combinations, 14 different mHags were recognized. The mHag HA-1, known to have a significant impact on the development of GVHD, was recognized in the two HA-1incompatible combinations. In one of these combinations, which was sex mismatched, all 56 clones analyzed were directed against HA-1, demonstrating the dominance of this mHag. In the four HA-1-compatible, sex-mismatched combinations, the anti-H-Y response was directed against one immunodominant epitope rather than against multiple Y-chromosome encoded epitopes. All male specific cytotoxic T lymphocytes (n=15) recognized the same high-performance liquid chromatography-purified peptide fraction presented by T2 cells. Moreover, all cytotoxic T lymphocytes tested (n = 6) were specific for the SMCY-derived peptide FIDSYICQV, originally described as being the H-Y epitope recognized in the context of HLA-A*0201. Conclusions. Some histocompatibility antigens are recognized in an immunodominant fashion and will therefore be recognized

in the majority of mismatched combinations. Only for such antigens, correlations between mismatches and the occurrence of GVHD or graft rejections will be found.

L7 ANSWER 9 OF 9 MEDLINE on STN DUPLICATE 5
1999036482. PubMed ID: 9820596. Genomic identification of the minor histocompatibility antigen HA-1 locus by allele-specific PCR. Wilke M; Pool J; den Haan J M; Goulmy E. (Department of Immunohematology and Bloodbank, Leiden University Medical Center, The Netherlands.. ihbsecr@euronet.nl) . Tissue antigens, (1998 Oct) Vol. 52, No. 4, pp. 312-7. Journal code: 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.

AB Graft-versus-host disease (GvHD) can be a major complication of allogeneic bone marrow transplantation even in recipients of HLA genotype-identical transplants. Disparities in minor histocompatibility antigens (mHags) between donor and recipient are a potential risk for the development of GvHD. A mismatch for the mHag HA-1 can cause GvHD in adult recipients of allogeneic bone marrow from HLA-identical donors. The mHag HA-1, first identified by HLA-A*0201-restricted **cytotoxic T cells** (CTLs), was recently chemically characterized as a nonapeptide. On the cDNA level, the HA-1 locus has two alleles, HA-1H and HA-1R, which differ in two nucleotides, resulting in a single amino acid substitution. Here we report on the genomic structure of the HA-1 locus. Isolation and sequencing of cosmid DNA encoding the **HA-1 peptide** sequence revealed that the HA-1 alleles are encoded by two exons. Two different primer sets were designed, each consisting of allele-specific primers and a common primer, and both sets containing intronic sequences. We performed genomic DNA typing of three families consisting of 24 HLA-A*0201-positive individuals. The predicted allele-specific products correlated in all cases with the mHag classification by CTLs and by RT-PCR. We demonstrate for the first time the genomic identification of the mHag HA-1 locus. Prospective genomic typing for the HA-1 alleles will improve donor selection and identify HLA-A*0201-positive recipients with a high risk for HA-1-induced GvHD.

=> s l1 and antigen presenting cell
L8 5 L1 AND ANTIGEN PRESENTING CELL

=> dup remove l8
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L9 1 DUP REMOVE L8 (4 DUPLICATES REMOVED)

=> d l9 cbib abs

L9 ANSWER 1 OF 1 MEDLINE on STN DUPLICATE 1
2004305073. PubMed ID: 15031203. Artificial antigen-presenting constructs efficiently stimulate minor histocompatibility antigen-specific cytotoxic T lymphocytes. Oosten Liesbeth E M; Blokland Els; van Halteren Astrid G S; Curtsinger Julie; Mescher Matthew F; Falkenburg J H Frederik; Mutis Tuna; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. l.e.m.oosten@lumc.nl) . Blood, (2004 Jul 1) Vol. 104, No. 1, pp. 224-6. Electronic Publication: 2004-03-18. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes (CTLs) specific for hematopoietic-restricted minor histocompatibility antigens (mHags) are important reagents for adoptive immunotherapy of relapsed leukemia after allogeneic stem cell transplantation. However, expansion of these CTLs to therapeutic numbers is often hampered by the limited supply of **antigen-presenting cells** (APCs). Therefore, we evaluated whether cell-sized latex beads coated with HLA/mHag complexes HLA-A2/HA-1 or HLA-A2/HA-2 and recombinant CD80 and CD54 molecules can replace professional APCs. The artificial antigen-presenting constructs (aAPCs) effectively stimulated HA-1- and HA-2-specific CTL clones as shown by

ligand-specific expansion, cytokine production, and maintenance of cytotoxic activity, without alteration of CTL phenotype. Furthermore, HA-1-specific polyclonal CTL lines were enriched as efficiently by aAPCs as by autologous **HA-1 peptide**-pulsed dendritic cells. Thus, aAPCs coated with HLA/mHag complexes, CD80, and CD54 may serve as tools for in vitro enrichment of immunotherapeutic mHag-specific CTL lines.

=> s l1 and peptide pulsed
L10 10 L1 AND PEPTIDE PULSED

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L11 3 DUP REMOVE L10 (7 DUPLICATES REMOVED)

=> d l11 1-3 cbib abs

L11 ANSWER 1 OF 3 MEDLINE on STN DUPLICATE 1
2004305073. PubMed ID: 15031203. Artificial antigen-presenting constructs efficiently stimulate minor histocompatibility antigen-specific cytotoxic T lymphocytes. Oosten Liesbeth E M; Blokland Els; van Halteren Astrid G S; Curtsinger Julie; Mescher Matthew F; Falkenburg J H Frederik; Mutis Tuna; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. l.e.m.oosten@lumc.nl) . Blood, (2004 Jul 1) Vol. 104, No. 1, pp. 224-6. Electronic Publication: 2004-03-18. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

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L11 ANSWER 2 OF 3 MEDLINE on STN DUPLICATE 2
2002472540. PubMed ID: 12234166. Efficient induction of minor histocompatibility antigen HA-1-specific cytotoxic T-cells using dendritic cells retrovirally transduced with HA-1-coding cDNA. Mutis Tuna; Ghoreschi Kamran; Schrama Ellen; Kamp Janine; Heemskerk Mirjam; Falkenburg J H Frederik; Wilke Martina; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, (2002) Vol. 8, No. 8, pp. 412-9. Journal code: 9600628. ISSN: 1083-8791. Pub. country: United States. Language: English.

AB Cytotoxic T-cells (CTLs) specific for the hematopoietic system-restricted minor histocompatibility antigen (mHag) HA-1 efficiently lyse HA-1-positive leukemic cells without affecting nonhematopoietic cells. HA-1-specific CTLs are thus potential tools for adoptive immunotherapy of relapsed leukemia after HLA-matched-HA-1-mismatched stem cell transplantation (SCT). In vitro generation of HA-1-specific CTLs from SC donors is possible using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide** as stimulator cells. However, this approach requires at least 6 weeks of in vitro culturing under GMP

(good manufacturing practice) conditions. Our data show that in vitro induction of HA-1-specific CTLs is more rapid with the use of DCs that are retrovirally transduced with the HA-1 complementary DNA. Retrovirally transduced DCs showed functional and long-term stable expression of the HA-1 CTL epitope in primary CTL cultures. In 4 SC donors, HA-1-transduced DCs induced HA-1-specific CTLs in 14 to 21 days. The in vitro-generated CTL lines contained 6% to 9% T-cells that stained brightly with tetrameric HLA-A2/**HA-1 peptide** complexes (HA-1(A2)
tetramer) and showed significant lysis of HA-1+ leukemic cells. The CTL induction procedure using **peptide-pulsed** DCs was less
effective and required 28 to 35 days of T-cell culture. Thus, sustained presentation of mHag HA-1 by retrovirally transduced DCs facilitates the in vitro induction of HA-1-specific CTLs.

L11 ANSWER 3 OF 3 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
2001:312013 Document No.: PREV200100312013. Efficient in vitro induction of minor histocompatibility antigen HA-1 specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with HA-1 coding gene segment. Mutis, Tuna [Reprint author]; Wilke, Martina [Reprint author]; Ghoreschi, Kamran; Schrama, Ellen [Reprint author]; Kamp, Janine [Reprint author]; Heemskerk, Mirjam; Falkenburg, J. H. Frederik; Goulmy, Els [Reprint author]. Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 582a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The minor histocompatibility antigen (mHag) HA-1 is a hematopoietic system specific polymorphic antigen that can be recognized by cytotoxic T cells (CTLs) in the context of HLA-A2. HA-1 specific CTLs exhibit strong anti-leukemia reactivity by lysing HA-1 positive leukemic cells and their clonogenic precursors without affecting non-hematopoietic cells. Adoptive transfer of in vitro generated HA-1 specific CTLs into HA-1 positive patients with relapsed leukemia may therefore be curative with a low risk of graft versus host disease (GvHD). We have recently shown the feasibility of in vitro generation of HA-1 specific CTLs from HA-1 negative individuals using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide.** However, under GMP conditions,
HA-1 CTLs can not be generated from some donors using **peptide pulsed** DCs. We therefore investigated whether generation of HA-1 specific CTLs is more effective using DCs that are retrovirally transduced to express the HA-1 antigen. The 312 base pair gene segment coding for the HA-1 CTL epitope was cloned into the retroviral vector LZRS. This vector was transduced into several cell lines including CD34+ DC progenitors with 10-40% efficiency. All retrovirally transduced cells showed stable and functional expression of the HA-1 CTL epitope. CD34+ DC progenitors differentiated normally into immature DCs within 10-12 days and induced strong in vitro HA-1 specific CTL responses in four out of six HA-1 negative healthy unprimed individuals. The CTL lines contained 6-10% HA-1 specific CTLs as determined by HLA-A2/**HA-1**
peptide tetramers. The induction of HA-1 specific CTLs by retrovirally transduced DCs required only one or two rounds of restimulation whereas CTL induction by **peptide pulsed**
DCs required three to five rounds of restimulations. During the CTL induction, the retrovirally transduced DCs were detected at least seven days in the cultures and retained their immature phenotype. Our results demonstrate that retrovirally transduced immature DCs effectively induce HA-1 specific CTL responses through their continuous presentation of the HA-1 T cell epitope to unprimed T cell precursors.

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L12 7726 (GOULMY E?/AU OR HUNT D?/AU OR ENGELHARD V?/AU)

=> s l12 and HA-1 peptide
L13 37 L12 AND HA-1 PEPTIDE

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L14 10 DUP REMOVE L13 (27 DUPLICATES REMOVED)

=> d l14 1-10 cbib abs

L14 ANSWER 1 OF 10 MEDLINE on STN DUPLICATE 1
2005543541. PubMed ID: 16219579. Adult and cord blood T cells can acquire HA-1 specificity through HA-1 T-cell receptor gene transfer. Mommaas Bregje; van Halteren Astrid G S; Pool Jos; van der Veken Lars; Wieles Brigitte; Heemskerk Mirjam H M; **Goulmy Els.** (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.) Haematologica, (2005 Oct) Vol. 90, No. 10, pp. 1415-21. Journal code: 0417435. E-ISSN: 1592-8721. Pub. country: Italy. Language: English.

AB BACKGROUND AND OBJECTIVES: Minor histocompatibility antigen (mHag)-specific graft-versus-leukemia reactivities are observed following unselected donor lymphocyte infusion for the treatment of relapse after HLA-matched mHag-mismatched stem cell transplantation (SCT). Adoptive transfer of donor-derived ex vivo-generated HA-1-specific oligoclonal T cells or **HA-1 peptide** patient vaccination are currently being explored as curative tools for stem cell based immunotherapy of hematologic malignancies. Another treatment modality to eradicate residual leukemic cells after SCT is the transfer of the HA-1 hematopoietic-specific T-cell receptor (TCR) into cells from the stem cell donor. This strategy would be particularly useful in case of relapse after cord blood transplantation (CBT) and is explored in this study. DESIGN AND METHODS: HLA-A2(neg) adult peripheral blood and cord blood mononuclear cells were transduced with the genes encoding the HA-1 alpha and beta TCR chains derived from established HA-1 specific cytotoxic T lymphocyte clones. RESULTS: The T cells transduced with HA-1 TCR alpha beta showed consistent marker gene expression, but low staining with HLA-A2/HA-1 tetrameric complexes. They did, however, show hematopoietic-restricted cytolytic activity against HLA-A2(pos)/HA-1(pos) target cells, including leukemic cells. INTERPRETATION AND CONCLUSIONS: The low level of HA-1-specific tetramer staining of HA-1 TCR alpha beta transduced T cells may be caused by hybrid TCR formation of the transferred TCRalpha and beta chains with endogenous TCR alpha and beta chains. This may cause unwanted alloreactivity and requires attention. The HA-1 TCR alpha beta transduced T cells show that the HA-1 TCR can be functionally transferred into donor mononuclear cells, which can be exploited in immunotherapeutic settings of SCT and CBT for hematologic malignancies.

L14 ANSWER 2 OF 10 MEDLINE on STN DUPLICATE 2
2004305073. PubMed ID: 15031203. Artificial antigen-presenting constructs efficiently stimulate minor histocompatibility antigen-specific cytotoxic T lymphocytes. Oosten Liesbeth E M; Blokland Els; van Halteren Astrid G S; Curtsinger Julie; Mescher Matthew F; Falkenburg J H Frederik; Mutis Tuna; **Goulmy Els.** (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. l.e.m.oosten@lumc.nl) . Blood, (2004 Jul 1) Vol. 104, No. 1, pp. 224-6. Electronic Publication: 2004-03-18. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes (CTLs) specific for hematopoietic-restricted minor histocompatibility antigens (mHags) are important reagents for adoptive immunotherapy of relapsed leukemia after allogeneic stem cell transplantation. However, expansion of these CTLs to therapeutic numbers is often hampered by the limited supply of antigen-presenting cells (APCs). Therefore, we evaluated whether cell-sized latex beads coated with HLA/mHag complexes HLA-A2/HA-1 or HLA-A2/HA-2 and recombinant CD80 and CD54 molecules can replace professional APCs. The artificial

antigen-presenting constructs (aAPCs) effectively stimulated HA-1- and HA-2-specific CTL clones as shown by ligand-specific expansion, cytokine production, and maintenance of cytotoxic activity, without alteration of CTL phenotype. Furthermore, HA-1-specific polyclonal CTL lines were enriched as efficiently by aAPCs as by autologous **HA-1 peptide**-pulsed dendritic cells. Thus, aAPCs coated with HLA/mHag complexes, CD80, and CD54 may serve as tools for in vitro enrichment of immunotherapeutic mHag-specific CTL lines.

L14 ANSWER 3 OF 10 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN

2003107041 EMBASE Hematopoiesis-restricted minor histocompatibility antigens HA-1- or HA-2-specific T cells can induce complete remissions of relapsed leukemia. Marijt W.A.E.; Heemskerk M.H.M.; Kloosterboer F.M.; **Goulmy E.**; Kester M.G.D.; Van der Hoorn M.A.W.G.; Van Luxemburg-Heys S.A.P.; Hoogeboom M.; Mutis T.; Drijfhout J.W.; Van Rood J.J.; Willemze R.; Falkenburg J.H.F.. W.A.E. Marijt, Department of Hematology, Leiden University Medical Center, PO Box 9600, 2300 RC, Leiden, Netherlands. w.a.f.marijt@lumc.nl. Proceedings of the National Academy of Sciences of the United States of America Vol. 100, No. 5, pp. 2742-2747 4 Mar 2003. Refs: 45.
ISSN: 0027-8424. CODEN: PNASA6
Pub. Country: United States. Language: English. Summary Language: English.
Entered STN: 20030403. Last Updated on STN: 20030403

AB Donor lymphocyte infusion (DLI) into patients with a relapse of their leukemia or multiple myeloma after allogeneic stem cell transplantation (alloSCT) has been shown to be a successful treatment approach. The hematopoiesis-restricted minor histocompatibility antigens (mHAgs) HA-1 or HA-2 expressed on malignant cells of the recipient may serve as target antigens for alloreactive donor T cells. Recently we treated three mHAg HA-1- and/or HA-2-positive patients with a relapse of their disease after alloSCT with DLI from their mHAg HA-1- and/or HA-2-negative donors. Using HLA-A2/HA-1 and HA-2 peptide tetrameric complexes we showed the emergence of HA-1- and HA-2-specific CD8(+) T cells in the blood of the recipients 5-7 weeks after DLI. The appearance of these tetramer-positive cells was followed immediately by a complete remission of the disease and restoration of 100% donor chimerism in each of the patients. Furthermore, cloned tetramer-positive T cells isolated during the clinical response specifically recognized HA-1 and HA-2 expressing malignant progenitor cells of the recipient and inhibited the growth of leukemic precursor cells in vitro. Thus, HA-1- and HA-2-specific cytotoxic T lymphocytes emerging in the blood of patients after DLI demonstrate graft-versus-leukemia or myeloma reactivity resulting in a durable remission. This finding implies that in vitro generated HA-1- and HA-2-specific cytotoxic T lymphocytes could be used as adoptive immunotherapy to treat hematological malignances relapsing after alloSCT.

L14 ANSWER 4 OF 10 MEDLINE on STN DUPLICATE 3

2002459659. PubMed ID: 12218130. Identification of a novel HLA-B60-restricted T cell epitope of the minor histocompatibility antigen HA-1 locus. Mommaas Bregje; Kamp Janine; Drijfhout Jan-Wouter; Beekman Nico; Ossendorp Ferry; Van Veelen Peter; Den Haan Joke; **Goulmy Els**; Mutis Tuna. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.) Journal of immunology (Baltimore, Md. : 1950), (2002 Sep 15) Vol. 169, No. 6, pp. 3131-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The polymorphic minor histocompatibility Ag HA-1 locus encodes two peptides, HA-1(H) and HA-1(R), with a single amino acid difference. Whereas the immunogenicity of the HA-1(R) allele has not yet been shown, the nonameric HA-1(H) peptide induces HLA-A2-restricted cytotoxic T cells in vivo and in vitro. It is not known whether the mHag HA-1(H) or HA-1(R) associates with other HLA class I molecules. Therefore, the polymorphic regions of both HA-1 alleles were analyzed to identify HLA class I binding peptides that are properly processed by proteasomal degradation. Peptide

binding analyses were performed for all nonameric HA-1(H/R) peptides for binding to nine HLA class I molecules with >10% prevalence in the Caucasian population and for seven nonameric/decameric HA-1(H/R) peptides predicted to bind to HLA-A3, -B14, and -B60. Only the nonameric KECVL(H)/(R)DDL and decameric KECVL(H)/(R)DDLL peptides showed strong and stable binding to HLA-B60. In vitro digestion of 29-aa-long **HA-1 peptides** by purified 20S proteasomes revealed proper cleavage at the COOH termini of both HLA-B60 binding HA-1(H) and HA-1(R) peptides. In subsequent analyses, dendritic cells pulsed with the nonameric HA-1(R) peptide did not induce CTLs that recognize the natural HLA-B60/HA-1(R) ligand. In contrast, dendritic cells pulsed with the nonameric HA-1(H) peptide induced IFN-gamma-secreting T cells specific for the natural HLA-B60/HA-1(H) ligand in three HLA-B60(+) HA-1(RR) individuals, demonstrating the immunogenicity of the HLA-B60/HA-1(H) ligand. In conclusion, this study shows a novel HLA-B60-restricted T cell epitope of the minor histocompatibility Ag HA-1 locus.

L14 ANSWER 5 OF 10 MEDLINE on STN DUPLICATE 4

2002348185. PubMed ID: 12091347. Generation of minor histocompatibility antigen HA-1-specific cytotoxic T cells restricted by nonself HLA molecules: a potential strategy to treat relapsed leukemia after HLA-mismatched stem cell transplantation. Mutis Tuna; Blokland Els; Kester Michel; Schrama Ellen; **Goulmy Els.** (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Blood, (2002 Jul 15) Vol. 100, No. 2, pp. 547-52. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Successful stem cell transplantation (SCT) across HLA barriers can be performed with cord blood, megadoses of stem cells, or with nonmyeloablative conditioning strategies. Because the HLA-mismatched transplants are often T-cell depleted, leukemia relapse rates are high. Treatment of relapsed leukemia after HLA-mismatched SCT is difficult. A novel potential strategy to treat relapsed leukemia after HLA-mismatched SCT is the use of patients' mismatched HLA molecules as antigen-presenting molecules to generate hematopoietic system-specific cytotoxic T cells (CTLs) from the stem cell donor. Adoptive transfer of these hematopoietic system-specific CTLs that are restricted by nonself HLA molecules may eliminate leukemia without affecting the patient's nonhematopoietic cells or donor hematopoietic cells. We investigated the feasibility of this strategy using the hematopoietic system-specific minor histocompatibility antigen HA-1, which is known to induce HLA-A2-restricted CTLs. HLA-A2(-) peripheral blood mononuclear cells were stimulated with HLA-A2(+) T2 cells pulsed with synthetic **HA-1 peptide** or with dendritic cells transduced with the HA-1 cDNA. Tetrameric HLA-A2/**HA-1 peptide** complexes were used to monitor and enrich HA-1-specific CTLs. In the alloreactive cultures, HA-1-specific CTLs were enriched up to 7% by 3 rounds of antigen-specific stimulations and up to 87% by fluorescence-activated cell sorting of tetramer-positive T cells. The HA-1-specific CTLs showed specific lysis of the relevant target cells, including leukemic cells. Because the polyclonal CTL cultures also contained natural killer cells and allo-HLA-A2-specific CTLs, CTL clones were generated that showed the expected HA-1 specificity only. Thus, HA-1-specific CTLs restricted by nonself HLA-A2 molecules can be generated in an HLA-A2-mismatched setting.

L14 ANSWER 6 OF 10 MEDLINE on STN DUPLICATE 5

2002472540. PubMed ID: 12234166. Efficient induction of minor histocompatibility antigen HA-1-specific cytotoxic T-cells using dendritic cells retrovirally transduced with HA-1-coding cDNA. Mutis Tuna; Ghoreschi Kamran; Schrama Ellen; Kamp Janine; Heemskerk Mirjam; Falkenburg J H Frederik; Wilke Martina; **Goulmy Els.** (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, (2002) Vol. 8, No. 8, pp. 412-9. Journal code: 9600628.

ISSN: 1083-8791. Pub. country: United States. Language: English.

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L14 ANSWER 7 OF 10 MEDLINE on STN DUPLICATE 6

2002425399. PubMed ID: 12163564. The hematopoietic system-specific minor histocompatibility antigen HA-1 shows aberrant expression in epithelial cancer cells. Klein Christoph A; Wilke Martina; Pool Jos; Vermeulen Corine; Blokland Els; Burghart Elke; Krostina Sabine; Wendler Nicole; Passlick Bernward; Riethmueller Gert; **Goulmy Els.** (Department of Immunology, Klinikum Innenstadt, Ludwig-Maximilians University, 80336 Munich, Germany.. E.A.J.M.Goulmy@lumc.nl) . The Journal of experimental medicine, (2002 Aug 5) Vol. 196, No. 3, pp. 359-68. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB Allogeneic stem cell transplantation (SCT) can induce curative graft-versus-tumor reactions in patients with hematological malignancies and solid tumors. The graft-versus-tumor reaction after human histocompatibility leukocyte antigen (HLA)-identical SCT is mediated by alloimmune donor T cells specific for polymorphic minor histocompatibility antigens (mHags). Among these, the mHag HA-1 was found to be restricted to the hematopoietic system. Here, we report on the HA-1 ribonucleic acid expression by microdissected carcinoma tissues and by single disseminated tumor cells isolated from patients with various epithelial tumors. The **HA-1 peptide** is molecularly defined, as it forms an immunogenic peptide ligand with HLA-A2 on the cell membrane of carcinoma cell lines. HA-1-specific cytotoxic T cells lyse epithelial tumor cell lines in vitro, whereas normal epithelial cells are not recognized. Thus, HA-1-specific immunotherapy combined with HLA-identical allogeneic SCT may now be feasible for patients with HA-1(+) carcinomas.

L14 ANSWER 8 OF 10 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:312013 Document No.: PREV200100312013. Efficient in vitro induction of minor histocompatibility antigen HA-1 specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with HA-1 coding gene segment. Mutis, Tuna [Reprint author]; Wilke, Martina [Reprint author]; Ghoreschi, Kamran; Schrama, Ellen [Reprint author]; Kamp, Janine [Reprint author]; Heemskerk, Mirjam; Falkenburg, J. H. Frederik; **Goulmy, Els** [Reprint author]. Dept. of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 582a. print. Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

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specific polymorphic antigen that can be recognized by cytotoxic T cells (CTLs) in the context of HLA-A2. HA-1 specific CTLs exhibit strong anti-leukemia reactivity by lysing HA-1 positive leukemic cells and their clonogenic precursors without affecting non-hematopoietic cells. Adoptive transfer of in vitro generated HA-1 specific CTLs into HA-1 positive patients with relapsed leukemia may therefore be curative with a low risk of graft versus host disease (GvHD). We have recently shown the feasibility of in vitro generation of HA-1 specific CTLs from HA-1 negative individuals using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide.** However, under GMP conditions, HA-1 CTLs can not be generated from some donors using peptide pulsed DCs. We therefore investigated whether generation of HA-1 specific CTLs is more effective using DCs that are retrovirally transduced to express the HA-1 antigen. The 312 base pair gene segment coding for the HA-1 CTL epitope was cloned into the retroviral vector LZRS. This vector was transduced into several cell lines including CD34+ DC progenitors with 10-40% efficiency. All retrovirally transduced cells showed stable and functional expression of the HA-1 CTL epitope. CD34+ DC progenitors differentiated normally into immature DCs within 10-12 days and induced strong in vitro HA-1 specific CTL responses in four out of six HA-1 negative healthy unprimed individuals. The CTL lines contained 6-10% HA-1 specific CTLs as determined by HLA-A2/**HA-1 peptide** tetramers. The induction of HA-1 specific CTLs by retrovirally transduced DCs required only one or two rounds of restimulation whereas CTL induction by peptide pulsed DCs required three to five rounds of restimulations. During the CTL induction, the retrovirally transduced DCs were detected at least seven days in the cultures and retained their immature phenotype. Our results demonstrate that retrovirally transduced immature DCs effectively induce HA-1 specific CTL responses through their continuous presentation of the HA-1 T cell epitope to unprimed T cell precursors.

L14 ANSWER 9 OF 10 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

1998:511549 Document No.: PREV199800511549. HA-1 and the SMCY-derived peptide FIDSYICQV (H-Y) are immunodominant minor histocompatibility antigens after bone marrow transplantation. Rufer, Nathalie; Wolpert, Elisabeth; Helg, Claudine; Tiercy, Jean-Marie; Gratwohl, Alois; Chapuis, Bernard; Jeannet, Michel; **Goulmy, Els**; Roosnek, Eddy [Reprint author]. Unite d'Immunol. Transplantation, Hopital Cantonal Univ. Geneve, 24 rue Micheli-du-Crest, CH-1211 Geneve 14, Switzerland. Transplantation (Baltimore), (Oct. 15, 1998) Vol. 66, No. 7, pp. 910-916. print. CODEN: TRPLAU. ISSN: 0041-1337. Language: English.

AB Background. Allogeneic bone marrow donors can be incompatible at different levels. Even HLA-identical pairs will be still incompatible for numerous minor histocompatibility antigens (mHag). Nevertheless, some incompatibilities are found to be associated with an increased risk of graft-versus-host disease (GVHD), which could be related to the way the immune system recognizes these antigens. Methods. We determined the specificity of cytotoxic T-cell clones isolated during acute GVHD or during bone marrow graft rejection in patients (n=14) transplanted with marrow from donors who were histoincompatible for different minor and/or major histocompatibility antigens. Results. We found a clear hierarchy among the different types of histoincompatibilities. In three combinations mismatched for a class I allele, all 27 clones isolated during GVHD were specific for the incompatible HIA molecule. In the 11 class I-identical combinations, 14 different mHags were recognized. The mHag HA-1, known to have a significant impact on the development of GVHD, was recognized in the two HA-1incompatible combinations. In one of these combinations, which was sex mismatched, all 56 clones analyzed were directed against HA-1, demonstrating the dominance of this mHag. In the four HA-1-compatible, sex-mismatched combinations, the anti-H-Y response was directed against one immunodominant epitope rather than against multiple Y-chromosome encoded epitopes. All male specific cytotoxic T lymphocytes (n=15) recognized the same high-performance liquid chromatography-purified peptide fraction presented by T2 cells. Moreover,

all cytotoxic T lymphocytes tested (n = 6) were specific for the SMCY-derived peptide FIDSYICQV, originally described as being the H-Y epitope recognized in the context of HLA-A*0201. Conclusions. Some histocompatibility antigens are recognized in an immunodominant fashion and will therefore be recognized in the majority of mismatched combinations. Only for such antigens, correlations between mismatches and the occurrence of GVHD or graft rejections will be found.

L14 ANSWER 10 OF 10 MEDLINE on STN DUPLICATE 7
1999036482. PubMed ID: 9820596. Genomic identification of the minor histocompatibility antigen HA-1 locus by allele-specific PCR. Wilke M; Pool J; den Haan J M; **Goulmy E.** (Department of Immunohematology and Bloodbank, Leiden University Medical Center, The Netherlands.. ihbsecr@euronet.nl) . Tissue antigens, (1998 Oct) Vol. 52, No. 4, pp. 312-7. Journal code: 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.

AB Graft-versus-host disease (GvHD) can be a major complication of allogeneic bone marrow transplantation even in recipients of HLA genotype-identical transplants. Disparities in minor histocompatibility antigens (mHags) between donor and recipient are a potential risk for the development of GvHD. A mismatch for the mHag HA-1 can cause GvHD in adult recipients of allogeneic bone marrow from HLA-identical donors. The mHag HA-1, first identified by HLA-A*0201-restricted cytotoxic T cells (CTLs), was recently chemically characterized as a nonapeptide. On the cDNA level, the HA-1 locus has two alleles, HA-1H and HA-1R, which differ in two nucleotides, resulting in a single amino acid substitution. Here we report on the genomic structure of the HA-1 locus. Isolation and sequencing of cosmid DNA encoding the **HA-1 peptide** sequence revealed that the HA-1 alleles are encoded by two exons. Two different primer sets were designed, each consisting of allele-specific primers and a common primer, and both sets containing intronic sequences. We performed genomic DNA typing of three families consisting of 24 HLA-A*0201-positive individuals. The predicted allele-specific products correlated in all cases with the mHag classification by CTLs and by RT-PCR. We demonstrate for the first time the genomic identification of the mHag HA-1 locus. Prospective genomic typing for the HA-1 alleles will improve donor selection and identify HLA-A*0201-positive recipients with a high risk for HA-1-induced GvHD.

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L15 25 L1 AND CTLS

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L16 6 DUP REMOVE L15 (19 DUPLICATES REMOVED)

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L16 ANSWER 1 OF 6 MEDLINE on STN DUPLICATE 1
2004305073. PubMed ID: 15031203. Artificial antigen-presenting constructs efficiently stimulate minor histocompatibility antigen-specific cytotoxic T lymphocytes. Oosten Liesbeth E M; Blokland Els; van Halteren Astrid G S; Curtsinger Julie; Mescher Matthew F; Falkenburg J H Frederik; Mutis Tuna; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. l.e.m.oosten@lumc.nl) . Blood, (2004 Jul 1) Vol. 104, No. 1, pp. 224-6. Electronic Publication: 2004-03-18. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Cytotoxic T lymphocytes (**CTLs**) specific for hematopoietic-restricted minor histocompatibility antigens (mHags) are important reagents for adoptive immunotherapy of relapsed leukemia after allogeneic stem cell transplantation. However, expansion of these **CTLs** to therapeutic numbers is often hampered by the limited supply of antigen-presenting cells (APCs). Therefore, we evaluated whether

cell-sized latex beads coated with HLA/mHag complexes HLA-A2/HA-1 or HLA-A2/HA-2 and recombinant CD80 and CD54 molecules can replace professional APCs. The artificial antigen-presenting constructs (aAPCs) effectively stimulated HA-1- and HA-2-specific CTL clones as shown by ligand-specific expansion, cytokine production, and maintenance of cytotoxic activity, without alteration of CTL phenotype. Furthermore, HA-1-specific polyclonal CTL lines were enriched as efficiently by aAPCs as by autologous **HA-1 peptide**-pulsed dendritic cells. Thus, aAPCs coated with HLA/mHag complexes, CD80, and CD54 may serve as tools for in vitro enrichment of immunotherapeutic mHag-specific CTL lines.

L16 ANSWER 2 OF 6 MEDLINE on STN DUPLICATE 2

2002459659. PubMed ID: 12218130. Identification of a novel HLA-B60-restricted T cell epitope of the minor histocompatibility antigen HA-1 locus. Mommaas Bregje; Kamp Janine; Drijfhout Jan-Wouter; Beekman Nico; Ossendorp Ferry; Van Veelen Peter; Den Haan Joke; Goulmy Els; Mutis Tuna. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, Leiden, The Netherlands.) Journal of immunology (Baltimore, Md. : 1950), (2002 Sep 15) Vol. 169, No. 6, pp. 3131-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The polymorphic minor histocompatibility Ag HA-1 locus encodes two peptides, HA-1(H) and HA-1(R), with a single amino acid difference. Whereas the immunogenicity of the HA-1(R) allele has not yet been shown, the nonameric HA-1(H) peptide induces HLA-A2-restricted cytotoxic T cells in vivo and in vitro. It is not known whether the mHag HA-1(H) or HA-1(R) associates with other HLA class I molecules. Therefore, the polymorphic regions of both HA-1 alleles were analyzed to identify HLA class I binding peptides that are properly processed by proteasomal degradation. Peptide binding analyses were performed for all nonameric HA-1(H/R) peptides for binding to nine HLA class I molecules with >10% prevalence in the Caucasian population and for seven nonameric/decameric HA-1(H/R) peptides predicted to bind to HLA-A3, -B14, and -B60. Only the nonameric KECVL(H)/(R)DDL and decameric KECVL(H)/(R)DDLL peptides showed strong and stable binding to HLA-B60. In vitro digestion of 29-aa-long **HA-1 peptides** by purified 20S proteasomes revealed proper cleavage at the COOH termini of both HLA-B60 binding HA-1(H) and HA-1(R) peptides. In subsequent analyses, dendritic cells pulsed with the nonameric HA-1(R) peptide did not induce **CTLs** that recognize the natural HLA-B60/HA-1(R) ligand. In contrast, dendritic cells pulsed with the nonameric HA-1(H) peptide induced IFN-gamma-secreting T cells specific for the natural HLA-B60/HA-1(H) ligand in three HLA-B60(+) HA-1(RR) individuals, demonstrating the immunogenicity of the HLA-B60/HA-1(H) ligand. In conclusion, this study shows a novel HLA-B60-restricted T cell epitope of the minor histocompatibility Ag HA-1 locus.

L16 ANSWER 3 OF 6 MEDLINE on STN DUPLICATE 3

2002348185. PubMed ID: 12091347. Generation of minor histocompatibility antigen HA-1-specific cytotoxic T cells restricted by nonself HLA molecules: a potential strategy to treat relapsed leukemia after HLA-mismatched stem cell transplantation. Mutis Tuna; Blokland Els; Kester Michel; Schrama Ellen; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Blood, (2002 Jul 15) Vol. 100, No. 2, pp. 547-52. Journal code: 7603509. ISSN: 0006-4971. Pub. country: United States. Language: English.

AB Successful stem cell transplantation (SCT) across HLA barriers can be performed with cord blood, megadoses of stem cells, or with nonmyeloablative conditioning strategies. Because the HLA-mismatched transplants are often T-cell depleted, leukemia relapse rates are high. Treatment of relapsed leukemia after HLA-mismatched SCT is difficult. A novel potential strategy to treat relapsed leukemia after HLA-mismatched SCT is the use of patients' mismatched HLA molecules as antigen-presenting molecules to generate hematopoietic system-specific cytotoxic T cells (

CTLs) from the stem cell donor. Adoptive transfer of these hematopoietic system-specific **CTLs** that are restricted by nonself HLA molecules may eliminate leukemia without affecting the patient's nonhematopoietic cells or donor hematopoietic cells. We investigated the feasibility of this strategy using the hematopoietic system-specific minor histocompatibility antigen HA-1, which is known to induce HLA-A2-restricted **CTLs.** HLA-A2(-) peripheral blood mononuclear cells were stimulated with HLA-A2(+) T2 cells pulsed with synthetic **HA-1 peptide** or with dendritic cells transduced with the HA-1 cDNA. Tetrameric HLA-A2/**HA-1 peptide** complexes were used to monitor and enrich HA-1-specific **CTLs.** In the alloreactive cultures, HA-1-specific **CTLs** were enriched up to 7% by 3 rounds of antigen-specific stimulations and up to 87% by fluorescence-activated cell sorting of tetramer-positive T cells. The HA-1-specific **CTLs** showed specific lysis of the relevant target cells, including leukemic cells. Because the polyclonal CTL cultures also contained natural killer cells and allo-HLA-A2-specific **CTLs**, CTL clones were generated that showed the expected HA-1 specificity only. Thus, HA-1-specific **CTLs** restricted by nonself HLA-A2 molecules can be generated in an HLA-A2-mismatched setting.

L16 ANSWER 4 OF 6 MEDLINE on STN DUPLICATE 4

2002472540. PubMed ID: 12234166. Efficient induction of minor histocompatibility antigen HA-1-specific cytotoxic T-cells using dendritic cells retrovirally transduced with HA-1-coding cDNA. Mutis Tuna; Ghoreschi Kamran; Schrama Ellen; Kamp Janine; Heemskerk Mirjam; Falkenburg J H Frederik; Wilke Martina; Goulmy Els. (Department of Immunohematology and Blood Transfusion, Leiden University Medical Center, The Netherlands.. t.mutis@lumc.nl) . Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation, (2002) Vol. 8, No. 8, pp. 412-9. Journal code: 9600628. ISSN: 1083-8791. Pub. country: United States. Language: English.

AB Cytotoxic T-cells (**CTLs**) specific for the hematopoietic system-restricted minor histocompatibility antigen (mHag) HA-1 efficiently lyse HA-1-positive leukemic cells without affecting nonhematopoietic cells. HA-1-specific **CTLs** are thus potential tools for adoptive immunotherapy of relapsed leukemia after HLA-matched-HA-1-mismatched stem cell transplantation (SCT). In vitro generation of HA-1-specific **CTLs** from SC donors is possible using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide** as stimulator cells. However, this approach requires at least 6 weeks of in vitro culturing under GMP (good manufacturing practice) conditions. Our data show that in vitro induction of HA-1-specific **CTLs** is more rapid with the use of DCs that are retrovirally transduced with the HA-1 complementary DNA. Retrovirally transduced DCs showed functional and long-term stable expression of the HA-1 CTL epitope in primary CTL cultures. In 4 SC donors, HA-1-transduced DCs induced HA-1-specific **CTLs** in 14 to 21 days. The in vitro-generated CTL lines contained 6% to 9% T-cells that stained brightly with tetrameric HLA-A2/**HA-1 peptide** complexes (HA-1(A2) tetramer) and showed significant lysis of HA-1+ leukemic cells. The CTL induction procedure using peptide-pulsed DCs was less effective and required 28 to 35 days of T-cell culture. Thus, sustained presentation of mHag HA-1 by retrovirally transduced DCs facilitates the in vitro induction of HA-1-specific **CTLs.**

L16 ANSWER 5 OF 6 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN

2001:312013 Document No.: PREV200100312013. Efficient in vitro induction of minor histocompatibility antigen HA-1 specific cytotoxic T-lymphocytes using dendritic cells retrovirally transduced with HA-1 coding gene segment. Mutis, Tuna [Reprint author]; Wilke, Martina [Reprint author]; Ghoreschi, Kamran; Schrama, Ellen [Reprint author]; Kamp, Janine [Reprint author]; Heemskerk, Mirjam; Falkenburg, J. H. Frederik; Goulmy, Els [Reprint author]. Dept. of Immunohematology and Blood Transfusion, Leiden

University Medical Center, Leiden, Netherlands. Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 582a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971. Language: English.

AB The minor histocompatibility antigen (mHag) HA-1 is a hematopoietic system specific polymorphic antigen that can be recognized by cytotoxic T cells (**CTLs**) in the context of HLA-A2. HA-1 specific **CTLs** exhibit strong anti-leukemia reactivity by lysing HA-1 positive leukemic cells and their clonogenic precursors without affecting non-hematopoietic cells. Adoptive transfer of in vitro generated HA-1 specific **CTLs** into HA-1 positive patients with relapsed leukemia may therefore be curative with a low risk of graft versus host disease (GvHD). We have recently shown the feasibility of in vitro generation of HA-1 specific **CTLs** from HA-1 negative individuals using dendritic cells (DCs) pulsed with synthetic **HA-1 peptide.** However, under GMP conditions, HA-1 **CTLs** can not be generated from some donors using peptide pulsed DCs. We therefore investigated whether generation of HA-1 specific **CTLs** is more effective using DCs that are retrovirally transduced to express the HA-1 antigen. The 312 base pair gene segment coding for the HA-1 CTL epitope was cloned into the retroviral vector LZRS. This vector was transduced into several cell lines including CD34+ DC progenitors with 10-40% efficiency. All retrovirally transduced cells showed stable and functional expression of the HA-1 CTL epitope. CD34+ DC progenitors differentiated normally into immature DCs within 10-12 days and induced strong in vitro HA-1 specific CTL responses in four out of six HA-1 negative healthy unprimed individuals. The CTL lines contained 6-10% HA-1 specific **CTLs** as determined by HLA-A2/**HA-1 peptide** tetramers. The induction of HA-1 specific **CTLs** by retrovirally transduced DCs required only one or two rounds of restimulation whereas CTL induction by peptide pulsed DCs required three to five rounds of restimulations. During the CTL induction, the retrovirally transduced DCs were detected at least seven days in the cultures and retained their immature phenotype. Our results demonstrate that retrovirally transduced immature DCs effectively induce HA-1 specific CTL responses through their continuous presentation of the HA-1 T cell epitope to unprimed T cell precursors.

L16 ANSWER 6 OF 6 MEDLINE on STN DUPLICATE 5

1999036482. PubMed ID: 9820596. Genomic identification of the minor histocompatibility antigen HA-1 locus by allele-specific PCR. Wilke M; Pool J; den Haan J M; Goulmy E. (Department of Immunohematology and Bloodbank, Leiden University Medical Center, The Netherlands.. ihbsecr@euronet.nl) . Tissue antigens, (1998 Oct) Vol. 52, No. 4, pp. 312-7. Journal code: 0331072. ISSN: 0001-2815. Pub. country: Denmark. Language: English.

AB Graft-versus-host disease (GvHD) can be a major complication of allogeneic bone marrow transplantation even in recipients of HLA genotype-identical transplants. Disparities in minor histocompatibility antigens (mHags) between donor and recipient are a potential risk for the development of GvHD. A mismatch for the mHag HA-1 can cause GvHD in adult recipients of allogeneic bone marrow from HLA-identical donors. The mHag HA-1, first identified by HLA-A*0201-restricted cytotoxic T cells (**CTLs**), was recently chemically characterized as a nonapeptide. On the cDNA level, the HA-1 locus has two alleles, HA-1H and HA-1R, which differ in two nucleotides, resulting in a single amino acid substitution. Here we report on the genomic structure of the HA-1 locus. Isolation and sequencing of cosmid DNA encoding the **HA-1 peptide** sequence revealed that the HA-1 alleles are encoded by two exons. Two different primer sets were designed, each consisting of allele-specific primers and a common primer, and both sets containing intronic sequences. We performed genomic DNA typing of three families consisting of 24 HLA-A*0201-positive individuals. The predicted

allele-specific products correlated in all cases with the mHag classification by **CTLs** and by RT-PCR. We demonstrate for the first time the genomic identification of the mHag HA-1 locus. Prospective genomic typing for the HA-1 alleles will improve donor selection and identify HLA-A*0201-positive recipients with a high risk for HA-1-induced GvHD.

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☐	L17	L15 and VLXDDLLEA	1
☐	L16	L15 and HA-1	4
☐	L15	530/328.ccls.	2486
☐	L14	L13 and HA-1	1
☐	L13	424/184.1.ccls.	2698
☐	L12	L11 and VLXDDLLEA	0
☐	L11	435/325.ccls.	19711
☐	L10	(mHag)adj(HA-1)	11
☐	L9	L8 and VLXDDLLEA	2
☐	L8	L7 and APC	32
☐	L7	L6 and pulsing	44
☐	L6	(process)same(cytotoxic)adj(T)adj(cell)	473
☐	L5	(HA-1)adj(peptide)	8
☐	L4	(engelhard)adj(victor)adj(H)	22
☐	L3	L2 and HA1	1
☐	L2	(hunt)adj(donald)adj(F)	31
☐	L1	(goulmy)adj(Els)adj(A)adj(J)adj(M)	6

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